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## COMPARATIVE STUDY OF SINGLE-DOSE AND THREE-DAY THERAPY FOR ACUTE UNCOMPLICATED CYSTITIS

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To assess the efficacy and safety of a single-dose therapy for acute uncomplicated cystitis (AUC), we compared 4 treatment regimens in 120 women. Patients eligible for the study were randomly assigned to one of four treatment groups: Ciprofloxacin (CPFX) 200 mg in a single oral dose (group A); 200 mg once daily for 3 days (group B); 200 mg twice daily for 3 day (group C); and cefpodoxime-proxetil (CPDX-PR) 200 mg once daily for 3 days (group D). The efficacy was evaluated 3 days after the single-dose therapy or at the end of a three-day therapy according to the criteria proposed by the Japanese UTI Committee.

The overall clinical efficacy in a total of 107 patients was evaluated to be excellent, moderate, and poor in 72 (67.3%), 35 (31.8%), and 1 (0.9%), respectively. The causative organisms were eradicated in 88.0, 85.2, 85.2, and 82.1% of the patients in groups A, B, C, and D, respectively. Recurrence was identified in 3 (2 in group A and one in group D) of 16 patients who were followed at 2 to 3 weeks after the treatment. No adverse reactions related to the antibiotics were recognized in the study. There were no significant differences in the clinical efficacy or recurrence rate among these four treatment regimens.

These results indicate that the single-dose therapy of CPFX is the treatment of choice in women with AUC.

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**Key words:** Acute uncomplicated cystitis, Single-dose treatment, Ciprofloxacin

### INTRODUCTION

Acute uncomplicated cystitis (AUC) is one of the most common bacterial infections among women. The selection of the most appropriate drug and regimen for urinary tract infections (UTIs) should be based on the site of infection, etiologic agent, complicating host factors, and history of the infection. Generally, AUC results from superficial bacterial infection of the bladder and urethra in women who have no underlying disorders or indwelling catheter in the urinary tract. More than 80 percent of the diseases are caused by *Escherichia coli*. These characteristics of the host and microorganisms in AUC seem to contribute to the general effectiveness of antimicrobial therapy for AUC.

Single-dose therapy for AUC has been studied extensively for 20 years. In the early 1990s, three to five days of treatment was recommended to be a reasonable alternative to a single-dose or longer-course treatment of AUC in several review articles<sup>1-4</sup>. However, more recently the efficacy of single-dose treatment with fluoroquinolones (FQs) has been reported to be equivalent to that of multiple-dose treatments with FQs or other classes of antibiotics<sup>5-9</sup>.

In order to assess the efficacy and safety of a single oral dose of ciprofloxacin (CPFX, 200 mg) for AUC, we compared it with three-day therapy with CPFX or

cefpodoxime-proxetil (CPDX-PR) in an open, multicenter trial.

### MATERIALS AND METHODS

#### *Study designs*

Between August 1993 and October 1994, we evaluated four treatment regimens for AUC in an open, multicenter study. Patients eligible for the study were randomly assigned to one of the following treatment groups; CPFX 200 mg in a single oral dose (group A); 200 mg once daily for 3 days (group B); 200 mg twice daily for 3 day (group C); and cefpodoxime-proxetil (CPDX-PR) 200 mg once daily for 3 days (group D). Informed consent obtained from all participants.

#### *Patient selection*

Criteria for inclusion of the study were women over 16 years of age; first visit within 10 days of onset of symptoms; symptoms (pain on urination) without fever over 37°C; pyuria of more than 10 leukocytes at a magnification of  $\times 400$  by sediment microscopy; and bacteriuria of more than  $10^4$  CFU/ml. Criteria for exclusion were a history of hypersensitivity to antimicrobial agents; antibiotic treatment during the preceding week; unusual isolates such as *Corynebacterium spp.*, *Lactobacillus spp.* which are usually not participating in the disease; known systemic disease such as diabetes mellitus and autoimmune disease;

known renal impairment (serum creatinine, >1.6 mg/dl); pregnancy or breast-feeding; and other concomitant infections.

#### Sampling and examinations

Midstream urine samples were obtained for urinalysis and urine culture. Additionally, urine samples were collected from 2 patients (case 1; 35 years old, body weight of 43 kg, case 2; 22 years old, body weight of 48 kg) with AUC after a single oral dose of CPFX (200 mg) to monitor urinary levels and renal excretion of CPFX for 24 hours.

Each dip-slide (Uricult E, Orion Diagnostica, Helsinki, Finland) used for quantitative urine culture was sent to the Department of Urology, Faculty of Medicine, Kagoshima University after overnight incubation at 37°C for further microbiological examinations. The isolated organisms were identified by standard bacteriologic methods. By using an agar dilution method<sup>10)</sup>, the minimum inhibitory concentrations (MICs) of ampicillin, cefaclor, CPDX-PR, ofloxacin (OFLX), and CPFX were determined against 105 strains isolated before treatment.

*Escherichia coli* Kp was used as a test strain for measurement of CPFX concentrations in urine samples by an agar-well method.

#### Evaluation of clinical efficacy and adverse effect

According to the Criteria for Evaluation of Clinical Efficacy of Antimicrobial Agents on UTI proposed by the Japanese UTI Committee (third edition)<sup>11)</sup>, the clinical and microbiological efficacy of the four treatment regimens were evaluated on day 5 (3 days after single-dose therapy or at the end of drug administration of three-day therapy). Overall clinical efficacy was evaluated as excellent, moderate, or poor including failure by combining the changes in 3 parameters; subjective symptoms (pain on urination), pyuria and bacteriuria.

A follow-up evaluation 2 to 3 weeks after completion of therapy was performed for the patient in whom the effect on bacteriuria was evaluated as "eliminated" in the first evaluation. All the patients enrolled in the study were assessed for adverse effects during the drug administration.

#### Statistical analysis

Statistical analysis was performed by the chi-square test or Fisher's exact test. A P value of less than 0.05 was considered statistically significant.

## RESULTS

Of 120 patients enrolled in the study, 117 including 10 with negative urine cultures completed the study and 3 did not return for a posttreatment visit. Therefore, the clinical efficacy was evaluable for 25, 27, 27, and 28 patients in groups A, B, C, and D, respectively. The mean age of these 107 patients was  $45.5 \pm 3.6$  (mean  $\pm$  S.E.) years with a range of 17 to 75.

Table 1. Patients' characteristics

	Treatment group*			
	A	B	C	D
No. of patients				
Enrolled	29	30	30	31
No bacteriuria or no return	4	3	3	3
Age				
Mean (yr)	43.6	48.5	46.2	45.6
Range	20-72	19-73	18-74	17-75
Menstrual status				
Premenopausal	13	12	13	15
Postmenopausal	12	15	14	13

\* A; Single oral dose of CPFX (200 mg), B; once daily of CPFX for 3 days, C; twice daily of CPFX for 3 days, D; once daily of CPDX-PR (200 mg).

There were no significant differences in the mean age, body weight, and menstrual state among the treatment groups (Table 1).

Before starting treatment, a total of 110 bacterial strains were isolated from 107 patients. *E. coli* (90%), *Staphylococcus spp.* (13%) and *Klebsiella pneumoniae* (4%) were predominant pathogens and no significant differences in the distribution of these pathogens was found among the groups (Table 2). The MICs of ampicillin, cefaclor, CPDX-PR, OFLX,

Table 2. Microbiological findings

Organisms isolated	Before treatment				After treatment*
	Treatment group				
	A	B	C	D	
<i>Staphylococcus spp.</i>	2	4	3	5	8
<i>Enterococcus faecalis</i>	0	0	0	1	5
<i>Escherichia coli</i>	20	21	23	22	0
<i>Klebsiella pneumoniae</i>	2	1	1	0	0
<i>Enterobacter cloacae</i>	0	0	1	0	1
<i>Enterobacter aerogenes</i>	0	1	0	0	0
<i>Proteus mirabilis</i>	1	0	0	1	1
<i>Proteus vulgaris</i>	0	0	0	1	0
<i>Serratia marcescens</i>	0	0	0	0	1
GNF-GNR**	0	0	0	0	1
Yeast-like organism	0	0	0	0	1

\* Bacteria appearing after treatment, regardless of bacterial cell count. \*\* GNF-GNR=glucose non-fermentative gram-negative rod.

Table 3. MICs of ampicillin, cefaclor, cepodoxime-proxetil, ofloxacin, and ciprofloxacin against 105 isolates

Antibiotics	MIC ( $\mu$ g/ml)		
	Range	MIC <sub>50</sub>	MIC <sub>90</sub>
Ampicillin	0.10->200	3.13	200
Cefaclor	0.10->200	3.13	100
Cepodoxime-proxetil	$\leq 0.025$ -200	0.20	3.13
Ofloxacin	$\leq 0.025$ -100	0.05	0.39
Ciprofloxacin	$\leq 0.025$ -100	$\leq 0.025$	0.39

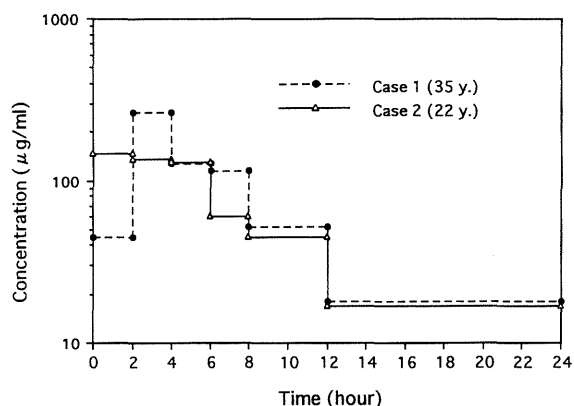


Fig. 1. Urinary levels of ciprofloxacin in two patients with acute uncomplicated cystitis.

and CPFX against 105 isolates including 83 strains of *E. coli* are summarized in Table 3. Of these antimicrobial agents, both OFLX and CPFX showed the most potent antimicrobial activity and inhibited the growth of more than 97% of the strains at the concentration of 3.13 µg/ml. Approximately, 20% of the strains were resistant to ampicillin and cefaclor.

The urinary levels of CPFX determined in two patients were variable. However, the level was over 40 µg/ml for 12 hours and over 15 µg/ml for 24 hours; approximately 30% of the drug was excreted in the urine within 24 hours after a 200 mg single oral dose (Fig. 1).

The causative organisms were eliminated in 22 out of 25 patients (88.0%) in group A, 23 out of 27 (85.2%) in group B and C, and 23 out of 28 (82.1%) in group D. The overall clinical efficacy was evaluated to be excellent, moderate, and poor in 71 (66.4%), 35 (32.7%), and 1 (0.9%) of the 107 patients (Table 4), respectively. Of 91 patients with negative urine culture at the end of antimicrobial administration, 16 patients returned 2 to 3 weeks after completion of therapy and recurrence (reinfection) was identified in 3 of them (two in group A and one in group D).

Adverse reactions related to the antibiotics were not found in any of the 117 patients who completed the study except for 3 patients who did not return for a posttreatment visit.

Statistical analysis showed no significant diffe-

rences in the clinical and microbiological efficacy on day 5 and the recurrence rate among these four treatment groups.

## DISCUSSION

In previous reviews of the treatment of UTIs, unacceptable failure or relapse occurred more frequently in the patients treated with a single-dose regimen of sulfamethazole-trimethprim or beta-lactam antibiotics than in those treated with a multiple-dose regimen of respective drugs<sup>1-4</sup>. However, later studies showed that a single-dose therapy with FQs gave a clinical and microbiological cure rate of more than 80%<sup>5-9</sup>.

In the present study, we compared the clinical efficacy of the single oral dose of CPFX with three-day regimens of CPFX or CPDX-PR. The study was conducted and evaluated according to the Criteria (third edition) proposed by Japanese UTI Committee<sup>11</sup>. The evaluation 3 days after the single oral dose of CPFX or at the end of drug administration of a three-day therapy revealed no significant differences in clinical and microbiological efficacy among the treatment groups.

Since the recurrence is not infrequent in women with AUC, follow-up evaluation several weeks after completion of therapy may be necessary. Despite our efforts to carry out the follow-up evaluation whenever possible, only 16 out of 91 patients in whom the effect on bacteriuria was evaluated as "eliminated" at the first evaluation returned for the follow-up evaluation 2 to 3 weeks after the completion of therapy. From our previous experiences we suppose that the resolution of subjective symptoms is the main reason why the patients do not return for the follow-up evaluation, but the true reason is not clear. Aside from the follow-up evaluation, the results of the present study indicate that the efficacy of a single-dose therapy with CPFX is equal to that of a three-day therapy with CPFX or CPDX-PR.

The antimicrobial agents used for the single dose therapy for AUC naturally need antimicrobial activity to cover the spectrum of common pathogens found in the clinical settings. In addition, long half-

Table 4. Clinical and microbiological responses

Efficacy	Treatment group			
	A	B	C	D
Microbiological evaluation				
Eliminated (%)	22 (88.0)	23 (85.2)	23 (85.2)	23 (82.1)
Decreased or replaced	3	4	3	3
Unchanged Evaluated			1	2
Overall clinical efficacy				
Excellent (%)	16 (64.0)	21 (77.8)	17 (63.0)	18 (64.3)
Moderate	9	6	9	10
Poor			1	

time in urine, sufficient urine concentration over MICs of pathogens, and post-antibiotic effect (PAE) seem desirable pharmacokinetic or pharmacodynamic parameters of the drugs.

FQs including CPFX meet most of these requirements for drugs used in a single-dose therapy. Although the increase of FQs resistance has been reported in several bacteria<sup>12,13</sup>, *E. coli*, the most common pathogen of AUC, is still susceptible to the FQs as demonstrated in this study. Depending on the concentration, FQs gave a 1-h to 4-h PAE against both gram-positive and gram-negative bacteria<sup>14</sup>, whereas most of the beta-lactam antibiotics demonstrate no PAE against gram-negative rods.

Bioavailability, renal excretion, and half-time may vary with the class of the FQs<sup>4</sup>, but it appears that urine concentrations over MICs of pathogens can be easily obtained by adjusting the dose of each drug. In the present study, the urine concentration of CPFX was over 40 µg/ml for 12 hours and over 17 µg/ml for 24 hours after a 200 mg oral dose. Taking the body weight of the enrolled patients and MICs of CPFX against the pathogens together with the urine concentrations into consideration, 200 mg of CPFX was the appropriate single dose in the present study.

In addition to these preferable pharmacokinetic or pharmacodynamic profiles of the FQs, the general advantages of a single-dose therapy with the FQs are lower cost, good tolerability, better compliance, and minimal alteration of normal bacterial flora, compared with multiple-dose therapy.

When a single-dose therapy with FQs fails to cure the patients with AUC, it may be reasonable to investigate the host factors complicating the infection such as a concomitant association of renal infection or functional or anatomical abnormalities in the urinary tracts.

### CONCLUSION

This study demonstrated that the efficacy of a single-dose therapy with CPFX is equal to that of a three-day treatment with CPFX or CPDX-PR for women with AUC. Single-dose therapy with FQs seems to be the treatment of choice in women with AUC.

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(迅速掲載)

## 和文抄録

## 女子急性単純性膀胱炎に対する単回治療と3日間治療の比較

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女子急性単純性膀胱炎に対する単回治療の有用性を明らかにする目的で，120例を対象に，ciprofloxacin (200 mg 錠) 単回 (A群)，1回3日間 (B群)，2回3日間 (C群)，ならびに cefpodoxime-proxetil (CPDX-PR) 200 mg 1回3日間 (D群) の4群間で，有効性と安全性を比較検討した。効果の判定は UTI 薬効評価基準 (第3版) に準じ，単回治療群では投薬3日後，3日間投与群では投薬終了翌日を原則とし，可能な範囲で投薬後2～3週間の再発の有無も検討した。評価可能な107例における総合臨床効果は著効72

例 (67.3%)，有効35例 (31.8%) 無効1例 (0.9%) であり，投薬後2～3週間の検討が可能であった16例中3例に再発が認められた。治療群別の細菌消失率は A群88%，B群85.2%，C群85.2%，D群82.1%であり，各群間の有効率に有意差はみとめられなかった。投与薬剤との関係が疑われる副作用の出現は1例もなかった。このらの結果から，ciprofloxacin (200 mg 錠) の単回投与は急性単純性膀胱炎の治療法として有用と考えられた。

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